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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,453	04/16/2001	Dan M. Granoff	CHIR-0283	1041

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Alisa A Harbin
Chiron Corporation
Intellectual Property R338
PO Box 8097
Emeryville, CA 94662

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,453	GRANOFF ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-29* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/09/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 03/09/06 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 03/09/06 in response to the final Office Action mailed 08/10/05. With this, Applicants have amended the claims.

Status of Claims

3) Claims 17 and 20 have been amended via the amendment filed 03/09/06.

Claims 17-29 are pending.

Claims 17-28 are under examination.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' Information Disclosure Statement filed 03/09/06. Except for the already cited reference(s), the information referred to therein has been considered and a signed copy is attached to this Office Action.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

7) The rejection of claims 17-23 and 25-27 made in paragraph 9 of the Office Action mailed 02/22/05 and maintained in paragraph 6 of the Office Action mailed 11/10/05 under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698,1992 - already of record)

and van der Voort *et al.* (*Infect. Immun.* 64: 2745-2751, 1996 - already of record) in view of Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996 - already of record), is withdrawn. A modified rejection is set forth below.

8) The rejection of claims 24 and 28 made in paragraph 10 of the Office Action mailed 02/22/05 and maintained in paragraph 7 of the Office Action mailed 11/10/05 under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698,1992 - already of record) as modified by van der Voort *et al.* (*Infect. Immun.* 64: 2745-2751, 1996 - already of record) and Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996 - already of record) as applied to claim 17 or 26 above, and further in view of Granoff (US 6,413,520, already of record) ('520), is withdrawn. A modified rejection is set forth below.

Applicant's arguments with respect to the above art rejections have been considered, but are moot in view of the withdrawal of, and/or the new ground(s) of art rejection(s) set forth below.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

9) Claims 17-28 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 17 is incorrect in the limitation 'an capsular' (see line 2). For the purpose of distinctly claiming the instant invention, it is suggested that Applicants replace the above-identified limitation with the limitation -- a capsular--.

(b) Claim 26 is confusing and/or inconsistent in scope with claim 17 with regard to the limitation 'an oligosaccharide'. For consistency and for the purpose of distinctly claiming the instant invention, it is suggested that Applicants replace the above-identified limitation with the limitation -- a capsular oligosaccharide--.

(c) Claims 18-25, 27 and 28, which depend from claim 17 or claim 26, are also rejected as being indefinite because of the indefiniteness identified above in the base claim(s).

Rejection(s) under 35 U.S.C § 103

10) Claims 17-19, 21-23 and 25 are rejected under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992 - already of record) in view of Dalseg *et al.* (*Vaccines* 96. (Ed) Brown F. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182,

1996).

Costantino *et al.* taught a conjugate vaccine comprising immunologically effective amounts of group C meningococcal oligosaccharides conjugated to CRM 197 and aluminium hydroxide, and a method of inducing an immune response to group C *Neisseria meningitidis* by administering an immunologically effective amount of the vaccine to a subject (see page 693).

Costantino *et al.* do not teach the use of outer membrane vesicles from a strain of group B *Neisseria meningitidis*, or from the specific strain 44/76 of group B *Neisseria meningitidis* in their conjugate vaccine.

However, Dalseg *et al.* taught an immunologically effective amount of an outer membrane vesicle (OMV) preparation from *N. meningitidis* strain 44/76 (B:15:P1.7, 16:L3,7,9) as a vaccine for patrenteral or intranasal use (see page 177; and 'Results and Discussion'). Dalseg *et al.* expressly taught that meningococcal OMVs have the ability to enhance the antibody responses when coadministered with a microbial antigen locally as well as at distant mucosal sites (see page 161).

Given Dalseg's express teaching that meningococcal OMVs have the ability to enhance the antibody response when coadministered with a microbial antigen locally as well as at distant mucosal sites in addition to serving as an immunogenic group B meningococcal vaccine, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine Dalseg's outer membrane vesicle preparation from the group B meningococcal reference strain H44/76 with Costantino's group C *Neisseria meningitidis* oligosaccharide-CRM_{197} conjugate vaccine to produce the instant invention, with a reasonable expectation of success. Adding an art-known adjuvant to an art-known immunogenic composition would have been well within the realm of routine experimentation as it has been routinely and conventionally practiced in the art without creating formulation challenges. Given its immune enhancing ability as taught by Dalseg, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of not only eliciting antibodies against Dalseg's immunogenic serogroup B meningococcal OMV, but also enhancing at the same time the antibody response to Costantino's serogroup C meningococcal glycoconjugate advantageously via a single immunogenic composition.

Claim 22 is a product-by-process claim which includes the process limitation: 'vesicles are produced by a deoxycholate extraction process'. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by

the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown that the underlying structure of the prior art group B meningococcal outer membrane vesicles differs from that of the instantly claimed vesicles.

Claims 17-19, 21-23 and 25 are *prima facie* obvious over the prior art of record.

11) Claims 17-19, 21-23 and 25 are rejected under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992 - already of record) and Dalseg *et al.* (*Vaccines* 96. (Ed) Brown F. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996) in view of Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996 - already of record).

Costantino *et al.* taught a conjugate vaccine comprising immunologically effective amounts of group C meningococcal oligosaccharides conjugated to CRM 197 and aluminium hydroxide, and a method of inducing an immune response to group C *Neisseria meningitidis* by administering an immunologically effective amount of the vaccine to a subject (see page 693).

Costantino *et al.* do not teach the use of outer membrane vesicles from a strain of group B *Neisseria meningitidis*, or from the specific strain 44/76 of group B *Neisseria meningitidis* in their conjugate vaccine.

However, Dalseg *et al.* taught an immunologically effective amount of an outer membrane vesicle (OMV) preparation from *N. meningitidis* strain 44/76 (B:15:P1.7, 16:L3,7,9) as a vaccine for patrenteral or intranasal use (see page 177; and 'Results and Discussion'). Dalseg *et al.* expressly taught that meningococcal OMVs have the ability to enhance the antibody responses when coadministered with a microbial antigen locally as well as at distant mucosal sites (see page 161).

Paradiso *et al.* taught that they have prepared immunogenic glycoconjugates of group C meningococcal saccharides covalently linked to the carrier CRM_{197} which elicited a booster

response characteristic of a T-dependent response in humans. Paradiso *et al.* further taught that since group B meningococcal capsule is not very immunogenic in people, the alternative approach of using outer membrane vesicles from a virulent group B meningococcal strain has been sought (see page 272). Paradiso *et al.* expressly taught that outer membrane vesicles prepared from group B meningococcal strains contain an array of proteins and lipids, and that in future, it will be desirable to mix them with a vaccine comprising group C meningococcal conjugate to create a new set of formulation (see paragraph bridging pages 272 and 273). The full passage bridging pages 272 and 273 of Paradiso *et al.* is provided below, with the relevant salient portion highlighted by italicization (see paragraph bridging pages 272 and 273):

> A significant portion of the morbidity from meningococcus is caused by group B. Unfortunately, the capsule from group B is not very immunogenic in people because of the similarity to saccharide structures on human cells. For this reason, and because of the potential for anti-group B antibody to cross-react with brain tissue, alternative approaches have been sought. *Most of the work has been done on outer membrane vesicles prepared from cells of virulent group B strains [10]. It seem likely that in the future it will be desirable to mix such a vaccine with the group C and/or group A conjugates.* Since these vesicle preparations contain an array of proteins and lipids, the combinations will create a new set of formulation challenges not unlike those encountered in mixing conjugate vaccines with DTP. [Emphasis added].

The key teaching or suggestion relevant to the instant rejection expressly taught by Paradiso *et al.* in 1996 is re-cited below with the motivational teaching highlighted by italicization:

> Most of the work has been done on *outer membrane vesicles* prepared from cells of virulent group B strains [10]. It seem likely that *in the future it will be desirable to mix such a vaccine with the group C and/or group A conjugates*. [Emphasis added].

Given Dalseg's express teaching that meningococcal OMVs have the ability to enhance the antibody response when coadministered with a microbial antigen locally as well as at distant mucosal sites in addition to serving as an immunogenic group B meningococcal vaccine, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine Dalseg's outer membrane vesicle vaccine from the group B meningococcal reference strain H44/76 with Costantino's group C *Neisseria meningitidis* oligosaccharide-CRM_{197} conjugate vaccine to produce the instant invention, with a reasonable expectation of success. Given Paradiso's express teaching in 1996 that it is desirable in future to mix a group C meningococcal conjugate with outer membrane vesicles prepared from group B meningococcal strains containing an array of proteins and lipids to create a new set of formulation, one of ordinary skill in the art would have been motivated to produce the instant invention in 1998 (i.e., well after the publication of Paradiso *et al.*) for the expected benefit of not only eliciting anti-group B meningococcal

antibodies against Dalseg's immunogenic serogroup B meningococcal OMV, but also enhancing at the same time the antibody response to Costantino's serogroup C meningococcal glycoconjugate advantageously via a single immunogenic composition.

Adding an art-known adjuvant to an art-known immunogenic composition would have been well within the realm of routine experimentation as it has been routinely and conventionally practiced in the art and would not have created new formulation challenges.

Claim 22 is a product-by-process claim, which includes the process limitation: 'vesicles are produced by a deoxycholate extraction process'. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown that the underlying structure of the prior art group B meningococcal outer membrane vesicles differs from that of the instantly claimed vesicles.

Claims 17-19, 21-23 and 25 are *prima facie* obvious over the prior art of record.

12) Claim 24 is rejected under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992 - already of record) as modified by Dalseg *et al.* (*Vaccines* 96. (Ed) Brown F. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996) and Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996 - already of record) as applied to claim 17 above, and further in view of Seid (US 6,638,513,) ('513).

The reference of Seid ('513) is used in this rejection because it qualifies as prior art under 35 U.S.C § 102(e) and therefore is not disqualified as prior art under 35 U.S.C § 103(a).

The teachings of Costantino *et al.* as modified by Dalseg *et al.* and Paradiso *et al.* are explained above, which do not teach their composition as further comprising polylactic acids or polyglycolic acids.

However, the use of polylactic acids or polyglycolic acids in combination with a meningococcal oligosaccharide conjugate was well known in the art at the time of the instant invention. For instance, Seid ('513) taught combining carriers, such as, polylactic or polyglycolic acids with meningococcal glycoconjugates for the purpose of primary vaccination wherein carriers do not themselves induce the production of harmful antibodies (see lines 10-18 in column 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Seid's ('513) polylactic or polyglycolic acid to Costantino's immunogenic composition as modified by Dalseg *et al.* and Paradiso *et al.* to produce the instant invention, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing Costantino's immunogenic composition as modified by Dalseg *et al.* and Paradiso *et al.* for primary vaccination without inducing the production of harmful antibodies as taught by Seid ('513).

Claim 24 is *prima facie* obvious over the prior art of record.

Relevant Prior Art

13) The following prior art publications document that proteosomic group B meningococcal outer membrane vesicles have been routinely mixed with other microbial antigens in a vaccine with no formulation challenges.

- Zollinger *et al.* (US 6,558,677, filed 10/15/1996) expressly disclosed covalent or non-covalent mixing of LPS of a Gram negative bacterial pathogen with the meningococcal native OMV proteosomes to enhance the immunogenicity of the LPS. See first full paragraph in column 8.

- Lowell *et al.* (US 6,476,201, filed 09/18/1995) expressly disclosed mixing of LPS of a Gram negative bacterial pathogen, such as, *S. flexneri* or *S. sonnei*, with the meningococcal native OMV proteosomes to enhance the immunogenicity of the LPS. See abstract; claims; and Examples.

- Lowell *et al.* (*J. Exp. Med.* 167: 658-663, 1988) taught the hybrophobic complexing of group B meningococcal polysaccharide with proteosomic OMP complexes (see page 658).

- Poolman *et al.* (*Antonie van Leeuwenhoek* 53: 413-419, 1987) taught mixing of detergent-extracted OMPs from the H44/76 meningococcal strain with group C meningococcal polysaccharide to produce a combined vaccine (see abstract; Materials and Methods; and Results).

Remarks

14) Claims 17-28 stand rejected.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

16) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

April, 2006

S. DEVI, PH.D.
PRIMARY EXAMINER